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US-PAT-NO: 5738985
DOCUMENT-IDENTIFIER: US 5738985 A

TITLE: Method for selective inactivation of viral replication

DATE-ISSUED: April 14, 1998

INVENTOR-INFORMATION:

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CLAIMS:

We claim:
1. A method for screening for a potential antiviral agent, comprising the steps of:
determining whether a potential antiviral agent interacts with a virus or cellular component which allows or prevents preferential translation of a virus RNA compared to a host RNA under virus infection conditions; and
determining whether any interaction of said agent: with said component reduces the level of translation of a RNA of said virus.
2. The method of claim 1, wherein said component is a protein or a nucleic acid.
3. The method of claim 1, wherein said component is a macromolecule selected from the group consisting of:
an RNA sequence domain, a DNA sequence domain, an initiation factor, and elongation factor, a termination factor, a transcription factor, a ribosomal protein, a glycosylase, a deglycosylase, a prenylating and deprenylating enzyme, a transferase, a polymerase, a synthetase, an ADP ribosylating enzyme, an ADP ribosylase, a kinase, a lipase, a myristylating or demyristylating enzyme, a phosphorylase, a protease, a rRNA, a tRNA, a ribonuclease, and a deoxyribonuclease.
4. The method of claim 1, wherein said component is a protein or a polypeptide, and said determining steps include providing said component in a translation mixture with RNA encoding a reporter polypeptide, and determining whether said agent alters expression of said reporter polypeptide in said mix.
5. The method of claim 1, wherein said component is selected

from the group consisting of:
a double-stranded RNA-activated protein kinase, and an inhibitor of a double-stranded RNA-activated protein kinase.
6. The method of claim 1, comprising the steps of:
forming a protein translation mixture which includes (i) a viral mRNA construct, said mRNA construct comprising an internal ribosome entry site (IRES) region and downstream of said IRES region, a first reporter protein coding region, (ii) ribosomes, and (iii) an agent to be tested,
incubating the components of the translation mixture under conditions effective to produce from the first reporter protein coding region a reporter protein,
and examining the mixture for the presence of reporter protein produced by such translation mixture,
wherein said agent is a potentially useful antivirus agent if the reporter protein produced in the presence of the test agent is less than an amount of reporter protein produced in the absence of said test agent.
7. The method of claim 1, further comprising the steps of:
forming a binding mixture comprising a cellular or viral translation initiation protein, an IRES element ribonucleotide sequence, and an agent to be tested,
incubating the components of the binding mixture under conditions effective to bind the initiation protein to the IRES element, and
examining the mixture for the presence of binding of the initiation protein to the IRES element;
wherein said agent is a useful anti virus agent if the extent of binding of the initiation protein to the IRES element is less than that observed in the absence of said agent.
8. The method of claim 2, wherein said component is virus encoded.
9. The method of claim 2, wherein said component is host cell encoded.
10. The method of claim 5, wherein said sequence domain is translationally linked to RNA encoding a reporter polypeptide, and said method further includes determining whether said agent alters the level of translation of said reporter polypeptide.
11. The method of claim 3, wherein said RNA sequence domain is selected from the group consisting of:
an IRES sequence, a 5'-untranslated region, a 3'-untranslated region, and an upstream open-reading frame sequence.
12. The method of claim 5, wherein said component is selected from the group consisting of:
p68 kinase, VAI RNA, TAR of HIV genome, EBER-1 RNA, and p58.
13. The method of claim 6, wherein the IRES region is derived from a picornavirus IRES region sequence.
14. The method of claim 6, wherein said IRES region is selected from the group consisting of an hepatitis A virus IRES sequence, an hepatitis B virus sequence and an hepatitis C virus IRES sequence.
15. The method of claim 6, wherein the protein translation mixture is a cell-free extract.
16. The method of claim 6, wherein the 5'-end of the viral mRNA construct includes a eukaryotic mRNA 5'-terminal cap and untranslated region (UTR) and downstream of said cap and UTR region, a second reporter protein.

17. The method of claim 13, wherein the IRES sequence is selected from the group consisting of an enterovirus, rhinovirus, cardiovirus, and aphthovirus IRES sequence.
18. The method of claim 16, wherein the translation mixture is contained in a cell.
19. The method of claim 7, wherein the cellular or viral translation initiation protein is selected from the group consisting of p52 and p57.
20. The method of claim 7, wherein the IRES element ribonucleotide sequence is derived from a picornavirus IRES region sequence.
21. The method of claim 7, wherein said IRES region is selected from the group consisting of an hepatitis A virus IRES sequence, an hepatitis B virus sequence and an hepatitis C virus IRES sequence.
22. The method of claim 7, wherein the cellular or viral translation initiation protein is bound to a solid support, the IRES element is labeled with a reporter, and said examining includes measuring the amount of reporter bound to the solid support.
23. The method of claim 7, wherein the IRES element RNA is bound to a solid support, the cellular or viral translation initiation protein is labeled with a reporter, and said examining includes measuring the amount of reporter bound to the solid support.
24. The method of claim 7, further including the step, after said incubating step, of adding to the incubation mixture an RNAase capable of cleaving free RNA but not protein bound RNA, and wherein said binding of the initiation protein to the IRES element is detected by the presence in the mixture of uncleaved IRES element RNA.
25. The method of claim 7, wherein said examining includes subjecting said mixture to a gel-shift electrophoresis assay.
26. The method of 7, wherein said incubating is carried out in solution phase, and said examining includes passing the mixture through a filter which retains said IRES element only when the element is bound to the cellular or viral translation initiation protein.
27. The method of claim 20, wherein the IRES sequence is selected from the group consisting of an enterovirus, rhinovirus, cardiovirus, and aphthovirus IRES sequence.
28. The method of claim 23, wherein a terminal region of said IRES element is bound to a complementary DNA sequence, and said DNA sequence is linked to the solid support.
29. A method for screening for a potential antiviral agent, comprising the steps of:
determining whether said agent is effective to inhibit viral replication in a host eukaryotic cell, where the virus produces an inhibitor which interferes with the activation or activity of the host-cell interferon-induced, double-stranded RNA-activated protein kinase, comprising
incubating a mixture containing the protein kinase, the viral inhibitor, and the agent to be tested under conditions effective to cause inhibitor interference with the activation or activity of the protein kinase, and
examining the mixture for such interference.
30. The method of claim 29, wherein the potential antiviral

agent inhibits replication in a host cell of a virus which produces an inhibitor able to bind to the protein kinase, to interfere with the activation of the protein kinase by double-stranded RNA, wherein said incubating includes incubating the protein kinase, viral inhibitor, and agent under conditions effective to bind the inhibitor to the protein kinase, and said examining includes examining the protein kinase for bound inhibitor.

31. The method of claim 30, wherein said incubating is carried out under conditions in which the protein kinase is autophosphorylated, in the absence of binding to the viral inhibitor, and said examining includes determining the extent of phosphorylation of the p68 kinase.

32. The method of claim 29, wherein the potential antiviral agent blocks viral replication of a virus which produces an inhibitor effective to activate a p58 host-cell protein which in activated form is effective to block activity or activation of the protein kinase, wherein the mixture formed includes the p58 host-cell protein, said incubating is carried out under conditions in which the protein kinase is activated in the absence of p58, and said examining includes examining the mixture for inhibition of protein kinase activity.

33. The method of claim 29, wherein the protein kinase and inhibitor are expressed in a yeast cell which is constructed to increase the expression of a reporter protein in the presence of activated protein kinase, and said examining includes examining the yeast cells for increased expression of the reporter protein.

34. A method for screening for a potential antiviral agent, comprising the steps of:

determining whether said agent is effective to inhibit viral replication in a host eukaryotic cell, where the host cell produces an inhibitor which interferes with the activation of the host-cell interferon-induced, double-stranded RNA-activated protein kinase, comprising

incubating a mixture containing the protein kinase, the host cell inhibitor, and the agent to be tested under conditions effective to cause inhibitor interference with the activation of the protein kinase, and

examining the mixture for such interference.

35. The method of claim 30, wherein said incubating is carried out in solution phase, and said examining includes passing the protein kinase, viral inhibitor, and test agent through a filter which retains the inhibitor only when the inhibitor is bound to the protein kinase.

36. The method of claim 30, wherein the protein kinase is bound to a solid support, the inhibitor is labeled with a reporter, and said examining includes measuring the amount of reporter bound to the solid support.

37. The method of claim 33, wherein the reporter protein is fused GCN4/.beta.-gal protein.

38. A yeast cell genetically engineered to express:

(a) a gene encoding a mammalian interferon-induced, double-stranded RNA-activated protein kinase,

(b) a reporter gene whose expression is increased by activation of the protein kinase, and

(c) a viral gene for producing a viral inhibitor able to block

activation of the protein kinase.
39. The yeast cell of claim 38, wherein the reporter gene is a fused GCN4/.beta.-gal gene.
40. A yeast cell genetically engineered to express:
(a) a gene encoding a mammalian interferon-induced, double-stranded RNA-activated protein kinase,
(b) a reporter gene whose expression in increased by activation of the protein kinase, and
(c) a gene encoding a mammalian protein induced or activated by a virus, which blocks activation of the mammalian interferon-induced, double-stranded RNA-activated protein kinase.